

### **Remarks**

Applicants note with appreciation the withdrawal of the rejection, in light of the amendment filed October 27, 2007, of claim 1 and 12 under 35 U.S.C. 112, 2<sup>nd</sup> paragraph; of claims 1-2, 10-13, and 14-15 under 35 U.S.C. 102(b) over Howarth et al.; and of claims 1 and 3-15 under 35 U.S.C. 103 over Liu et al.

By this paper, claims 1 and 31 have been amended and claim 3 is canceled. Support for the amendment is found, among other places, in the claims as originally filed. As such, no new matter is submitted by this amendment.

Currently, claims 1-2, 4-15, 23, and 31-33 are pending; and claims 16-22, 24-30, and 34 remain withdrawn.

Claims 1-2, 4-15, 23, and 31-33 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kumar *et al* (Tetrahedron letters, 1991, 32(16): 1901-1904; hereinafter *Kumar*). Claims 1-2, 10-11, 13-15, and 31-33 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter.

#### ***Rejection of Claim under 35 U.S.C. 102(b) over Kumar***

Claims 1-2, 4-15, 23, and 31-33 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Kumar*.

As stated in paragraph 8 on page 3 of the Office Action, *Kumar* relates to a new chemoenzymatic synthesis of optically pure (R)-tomoxetine and both the enantiomers of fluoxetine (see abstract). The Examiner believes that *Kumar* teaches Baker's yeast reduction of ethyl 3-oxo-3-phenylpropanoate (ketone body) to yield ethyl 3-hydroxy-3-phenylpropionate (alcohol), the step comprising Baker's yeast, glucose, and water (referring to page 1901, 3<sup>rd</sup> paragraph and page 1902, Scheme, step (i)). The Examiner therefore believes that *Kumar* reads

onto claims 1 and 14-15 because *Kumar* teaches the reduction of starting material which is a ketone into a final product which is alcohol, and thus the reaction must inherently have all of the features as claimed.

In the amendment dated October 27, 2007, Applicants stated that "glucose must likely be dissolved in the method of *Kumar* in order to be chemically useful" and thus the amount of water would be sufficient to dissolve the glucose in the reaction. In response, the Examiner is of the position that " since minimal amount of water is being used, it is inherent that glucose was dissolved in the water first before adding to the yeast." (Office Action, paragraph 10)

In paragraph 10 of the Office Action, the Examiner also points to the specification of the present application which describes reacting 10g of yeast with 10ml of water (see paragraphs [0075] and [0081]), 5g of yeast with 5ml of water (see paragraph [0079] and [0085]). By pointing out that *Kumar* further teaches the final products (R)-fluxetine and (S)-fluxetine as claimed in the present application, the Examiner therefore considers the reaction conditions taught by *Kumar* to be the same as the present application, "since water and yeast were used to reduce ketone to alcohol in step (i) to produce the alcohol precursor used to synthesize the final products."

For at least the reasons given below, Applicants respectfully submit that claims 1-2, 4-15, 23, and 31-33 are patentable under 35 U.S.C. 102(b) over *Kumar*.

Independent claim 1 in current form recites a method comprising "subjecting the organic compound to a yeast mediated reduction in the presence of an amount of water that is sufficient for enzymes to be hydrated and but insufficient to provide a visible separate water layer... wherein a water-to-yeast ratio is up to 1.5 ml/g." (Emphasis Added).

The Examiner's attention is directed to reference five (5) incorporated on page 1901 of *Kumar* with the reference titled "Asymmetric Reduction of Carbonyl Compounds by yeast II preparation of optically active  $\alpha$ - and  $\beta$ -Hydroxy Carboxylic Acid Derivatives" to Deol

et al. (hereinafter *Deol*). *Deol* is also submitted concurrently with a supplemental IDS for the record.

The *Deol* describes, in detail, the "Baker's yeast reduction" mentioned at page 1901, 3<sup>rd</sup> paragraph of *Kumar*. In particular, *Deol* in relevant portion provides:

Method A.-- A thick suspension of industrial yeast (100g of wet-packed Fermex brand, Fermentation Industries, Granville, N.S.W.), sucrose (100g) in water (600ml) was prepared and kept at room temperature until vigorous gas production ensued (about 30 min). (Emphasis Added)  
*Deol*, page 2464

From the experimental section of *Deol* cited above, it is clear that "wet packed Fermex" yeast is added to 600ml water to form a thick suspension. One skilled in the art would readily observe a water phase out of a 600 ml water mixture containing only 100g of yeast. As such, the water to yeast ratio of 600ml/100g or 6 ml/g taught in *Kumar* as detailed in *Deol* is far greater than the ratio of up to 1.5 ml/g as recited in claim 1. This drastic difference is confirmed by the Examiner that "the specification of the instant application describes 10g of yeast with 10ml of water" which equates to a water to yeast ratio of 10ml/10g or 1ml/g, whereas *Kumar* through the incorporated *Deol* reference teaches the water to yeast ratio of 6ml/g – a value six times the specific ratio of 1ml/g referenced by the Examiner.

Furthermore, the yeast reaction conditions described in *Deol* are typical for yeast reduction reactions, at least because yeast is known in the art to be live organisms and enzymatic activities associated thereof often require an ample supply of water. Therefore, one skilled in the art would not be motivated to provide a mere damping environment for a yeast reaction to take place whereas a water to yeast ratio is only up to 1.5 ml/g recited in claim 1 as amended.

By the operation of the invention embraced by the instant claim 1, a yeast mediated reduction is effectuated without laborious after-reaction step for water removal -- a step

often needed when excessive amount of water is present such as those yeast reactions in *Kumar*. Similarly, the method of claim 1 simplifies the isolation of a product compound by omitting the need for extensive water removal. In addition, due to the much simplified process of utilizing a yeast mediated reduction, the method of claim 1 greatly facilitates scale-up applications by reducing reagent consumption and operation costs.

In light of the above remarks, the rejection to claims 1-2, 4-15, 23, and 31-33 are believed to have been traversed. Reconsideration and withdrawal of the rejection to claims 1-2, 4-15, 23, and 31-33 under 35 U.S.C 102(b) over *Kumar* is solicited.

***Rejection of Claims 1-2, 10-11, 13-15,  
and 31-33 under 35 U.S.C. 112, 2<sup>nd</sup> Paragraph***

The Examiner believes that claims 1-2, 10-11, 13-15 and 31-33 are indefinite for failing to particularly point out and distinctly claim the subject matter which is regarded as the invention (Office Action, page 5).

In particular and in relation to rejecting claims 1-2, 10-11, and 13-15, the Examiner states that "it is unclear how one of ordinary skill in the art would know or determine how much water is sufficient to hydrate an enzyme but insufficient to provide a visible separate water layer ..."

In response, claim 1 has been amended to incorporate the limitation of the originally filed claim 3 and claim 1 as amended now recites a method comprising "subjecting the organic compound to a yeast mediated reduction in the presence of an amount of water ... wherein a water-to-yeast ratio is up to 1.5 ml/g."

By providing a water-to-yeast ratio of up to 1.5 ml/g, claim 1 in amended form and all the claims dependent therefrom are believed to have provided sufficient degree of clarity such that one skilled in the art should know or determine the amount of water sufficient to hydrate the yeast reaction.

In particular, claim 2 is rejected because the Examiner believes "it is unclear how much water would be enough . . . how much water is sufficient for yeast mediated reduction to take place, but insufficient to provide a visible separate water layer."

In response, it is submitted that requisite clarity as to the amount of water recited in claim 2 is believed to have been provided in light of the instant amendment to claim 1, from which claim 2 depends. Particularly, claim 2 would also read on the limitation of "wherein a water-to-yeast is up to 1.5 ml/g" as recited in claim 1 as amended. Further, contrary to the Examiner's belief cited above, the amount of water that is sufficient to enable yeast mediated reduction but "insufficient to provide a separate water layer" may be ascertained by, as one skilled in the art would, adding the water drop by drop till a separate water layer just becomes visible. Since generally 20 drops of water equal to about 1ml of water, there will be no undue experimentation where only countable drops of water are needed to be added; but rather one or two experiments would suffice to ascertain an exact number of water drops per a particular amount of yeast in grams. As such, claim 2 is submitted to be patentable under 35 U.S.C. 112, 2<sup>nd</sup> paragraph.

In addition, claim 31 is rejected for lack of clarity as the phrase "in the absence of a solvent" since the Examiner believes it is not clear whether the solvent includes water.

In response, claim 31 has been amended to read "in the absence of a solvent other than water." As such, the requisite clarity of claim 31 is believed to have been provided.

Reconsideration and withdrawal of rejection to claims 1-2, 10-11, 13-15, and 31-33 under 35 U.S.C. 112, 2<sup>nd</sup> paragraph is solicited.

### **Conclusion**

Applicants have made a genuine effort to respond to each of the Examiner's rejections in advancing the prosecution of this case. Applicants believe that all formal and substantive requirements for patentability have been met and that this case is in condition for

allowance, which action is respectfully requested. If a telephone or video conference would help expedite allowance or resolve any additional questions, such a conference is invited at the Examiner's convenience.

The Petition fee of \$60.00 is being charged to Deposit Account No. 02-3978 via electronic authorization submitted concurrently herewith. The Commissioner is hereby authorized to charge any additional fees or credit any overpayments as a result of the filing of this paper to Deposit Account No. 02-3978.

Respectfully submitted,

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Date: April 11, 2008

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